

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 217PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 30302	International filing date (day/month/year) 17/12/1999	(Earliest) Priority Date (day/month/year) 18/12/1998
Applicant AXYS PHARMACEUTICALS, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

(HETERO)ARYL-BICYCLIC HETEROARYL DERIVATIVES, THEIR PREPARATION AND THEIR USE AS PROTEASE INHIBITORS

5. With regard to the abstract,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/30302

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-3
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3

Due to the fact that the definition of the compounds of formula (I) is too general and/or encompasses too broad a range of different chemical groups (only partly supported by examples given in the description), the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (cf. Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.

Therefore the search was performed on the basis of the examples and those claims derived therefrom which are clear and concise, in combination with the alleged pharmaceutical use as protease inhibitors. The search report thus covers those compounds of formula (I) wherein A denotes either a benzimidazole or an indole moiety attached in 2-position to B being a substituted phenyl moiety, see claims 4, 5, 6(part), 7(part), 8, 12, 13 and 14 in combination with claims 11 or 16.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D235/18 A61K31/415 A61P7/02 C07D401/10 A61K31/44
C07D403/10 C07D471/04 C07D417/10 A61K31/425 C07D413/10
C07D407/10 C07D209/12 A61K31/40 C07D409/10 C07D407/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TIDWELL R.R. ET AL.: "Diarylamidine derivatives with one or both of the aryl moieties consisting of an indole or indole-like ring. Inhibitors of arginine-specific esterproteases" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 21, no. 7, 1 July 1978 (1978-07-01), pages 613-623, XP000573913 ISSN: 0022-2623 the whole document --- -/--	4-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

28. 06. 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/09 A61K31/66 //(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 114, no. 21, 27 May 1991 (1991-05-27) Columbus, Ohio, US; abstract no. 207259j, NISHI T. ET AL.: "Preparation of benzothiazoles and benzimidazoles as blood platelet aggregation inhibitors" page 832; column 1; XP002139445 abstract & JP 02 306916 A (OTSUKA PHARMACEUTICAL CO., LTD.; JAPAN) compounds 86-91 page 148 -page 149; table 2 --- -/-	4,6,9-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IWANOWICZ E.J. ET AL.: "Derivatives of 5-amidine indole as inhibitors of thrombin catalytic activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 6, no. 12, 18 June 1996 (1996-06-18), pages 1339-1344, XP004134837 ISSN: 0960-894X scheme 1 table 1	12,13, 15,16
X	--- WO 98 22619 A (ARRIS PHARMACEUTICAL CORPORATION & REGENTS OF UNIVERSITY OF CALIFORNIA) 28 May 1998 (1998-05-28) claims 32-44,48,52,54	4-16
P,X	--- WO 99 26933 A (AXYS PHARMACEUTICALS, INC.) 3 June 1999 (1999-06-03) compounds 22, 23 page 34; claims 1-7,9-11	4-7, 9-13,15, 16
A	--- KATZ B.A. ET AL.: "Design of potent selective zinc-mediated serine protease inhibitors" NATURE, GB, MACMILLAN JOURNALS LTD. LONDON, vol. 391, 5 February 1998 (1998-02-05), pages 608-612, XP002095430 ISSN: 0028-0836 compounds APD-4, APD-6, APD-8	4-16
P,A	--- WO 99 26941 A (AXYS PHARMACEUTICALS, INC.) 3 June 1999 (1999-06-03) compounds 1-7, 12-14, 18, 24-26, 28-30, 37, 42, 48-69, 84-88, 103-106, 108-110, 114-117 claims 1-8 -----	4-16

Information on patent family members

Int. Application No

PCT/US 99/30302

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 2306916	A	20-12-1990	JP 2869561 B	10-03-1999
WO 9822619	A	28-05-1998	AU 2336497 A	10-06-1998
			EP 0943008 A	22-09-1999
WO 9926933	A	03-06-1999	AU 1608399 A	15-06-1999
WO 9926941	A	03-06-1999	AU 1607299 A	15-06-1999



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 235/18, A61K 31/415, A61P 7/02, (continued on the following page)	A3	(11) International Publication Number: WO 00/35886 (43) International Publication Date: 22 June 2000 (22.06.00)
(21) International Application Number: PCT/US99/30302 (22) International Filing Date: 17 December 1999 (17.12.99) (30) Priority Data: 60/113,007 18 December 1998 (18.12.98) US (71) Applicant (for all designated States except US): AXYS PHARMACEUTICALS, INC. [US/US]; 180 Kimball Way, South San Francisco, CA 94080 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ALLEN, Darin, Arthur [US/US]; 519 Sierra Vista #3, Mountain View, CA 94043 (US). HATAYE, Jason, M. [US/US]; 574 Holyoke, San Francisco, CA 94134-1737 (US). HRUZEWICZ, Witold, N. [PL/US]; 1503 McKinnon Avenue, San Francisco, CA 94124 (US). KOLESNIKOV, Aleksandr [UA/US]; 1474 46th Avenue, San Francisco, CA 94122 (US). MACKMAN, Richard, Laurence [GB/US]; 2240 Bay Street, Apt. 302, San Francisco, CA 94403 (US). RAI, Roopa [IN/US]; 237 Clifton Avenue, San Carlos, CA 94070 (US). SPENCER, Jeffrey, R. [US/US]; 8 Baycrest Way, South San Francisco, CA 94080 (US). VERNER, Erik, J. [US/US]; 709 Catamaran Street, #1, Foster City, CA 94404 (US). YOUNG,		Wendy, B. [US/US]; 110 West 3rd Avenue #5, San Mateo, CA 94403 (US). (74) Agents: KATHARDEKAR, Vinit, G. et al.; Axys Pharmaceuticals, Inc., 180 Kimball Way, South San Francisco, CA 94080 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 26 October 2000 (26.10.00)
(54) Title: (HETERO)ARYL-BICYCLIC HETEROARYL DERIVATIVES. THEIR PREPARATION AND THEIR USE AS PROTEASE INHIBITORS (57) Abstract <p>The present invention provides novel compounds of the Formula (I): A-B, its prodrug forms, or pharmaceutically acceptable salts thereof, wherein A represents a saturated, unsaturated, or a partially unsaturated bicyclic heterocyclic ring structure, and B represents an aryl or a heteroaryl group. Preferred compounds of the present invention comprise a benzimidazole or indole nucleus. The compounds of this invention are inhibitors of serine proteases, Urokinase (uPA), Factor Xa (FXa), and/or Factor VIIa (FVIIa), and have utility as anti cancer agents and/or as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals.</p>		

(51) International Patent Classification:⁷ (continued)

C07D 401/10, 403/10, 471/04, 417/10, 413/10, 407/10, 409/10, 407/12, A61K 31/44, 31/425, 31/40, C07F 9/09, A61K 31/66 // (C07D 471/04, 235:00, 221:00)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

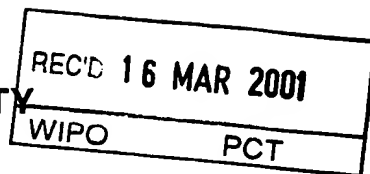
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
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CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



14

Applicant's or agent's file reference 217PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/30302	International filing date (day/month/year) 17/12/1999	Priority date (day/month/year) 18/12/1998
International Patent Classification (IPC) or national classification and IPC C07D235/00		
Applicant AXYS PHARMACEUTICALS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 14/07/2000	Date of completion of this report 14.03.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hartrampf, G Telephone No. +49 89 2399 8274 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/30302

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-165 as originally filed

Claims, No.:

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/30302

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-3,11,16.

because:

☒ the said international application, or the said claims Nos. 11,16 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-3.

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,7,8,14
	No:	Claims	4,6,9-13,15,16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4-16
Industrial applicability (IA)	Yes:	Claims	4-10,12-15

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/30302

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/30302

was

ad section III

1. As already indicated in the international search report, see PCT/ISA/210 claims 1 to 3 directed to compounds of formula (I) are so broadly defined that already a preliminary search retrieved too many relevant documents.
Due to the fact that no international search report has been established in that respect no preliminary examination will be made for claims 1 to 3, cf. Rule 66.1(3) PCT.
2. For the assessment of the present claims 11 and 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

ad section V

1. PRIOR ART

The following documents cited in the International search report were taken into consideration

- f D1: TIDWELL R.R. ET AL.: 'Diarylamidine derivatives with one or both of the aryl moieties consisting of an indole or indole-like ring. Inhibitors of arginine-specific esteroproteases' JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 21, no. 7, 1 July 1978, pages 613-623 *whole doc.*
- (f) D2: CHEMICAL ABSTRACTS, vol. 114, no. 21, 27 May 1991 Columbus, Ohio, US; abstract no. 207259j, NISHI T. ET AL.: 'Preparation of benzothiazoles *expts 86-91 p. 148-149 Table 2*

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/30302

and benzimidazoles as blood platelet aggregation inhibitors' page 832;
column 1; & JP 02 306916 A (OTSUKA PHARMACEUTICAL CO., LTD.)

7
Seheret
Table 1
D3: IWANOWICZ E.J. ET AL.: 'Derivatives of 5-amidine indole as inhibitors of
thrombin catalytic activity' BIOORGANIC & MEDICINAL CHEMISTRY
LETTERS, GB, OXFORD, vol. 6, no. 12, 18 June 1996, pages 1339-1344

x
D4: WO 98 22619 A (ARRIS PHARMACEUTICAL CORPORATION & REGENTS
OF UNIVERSITY OF CALIFORNIA) 28 May 1998 *claims 32-44, 48, 52, 54*

9, 17
D5: KATZ B.A. ET AL.: 'Design of potent selective zinc-mediated serine
protease inhibitors' NATURE, GB, MACMILLAN JOURNALS LTD. LONDON,
vol. 391, 5 February 1998, pages 608-612.

2. NOVELTY

Having regard to the compounds disclosed in the prior art cited above the subject-matter of the present application, i.e. (hetero)aryl-bicyclic heteroaryl derivatives of formula (I), does **not** appear to fulfil the requirements of novelty, cf. Article 33(2) PCT.

2.1. D1 describes *inter alia* antiproteolytic 2-phenyl-indole and 2-phenyl-benzimidazole derivatives, see compounds 1 to 13, 36 to 41, 49 and 50 which are comprised by present claims 4, 6, 9 to 12, 15 and 16.

D2 discloses *inter alia* blood platelet aggregation inhibiting 2-phenylbenzimidazole derivatives, see compounds 86 to 91 in the JP-patent document which are comprised by present claims 4, 6, 9 to 12, 15 and 16.

→ D3 comprises thrombin inhibiting 2-phenyl-indole derivatives, see compounds in scheme 1 and in table 1 which are comprised by present claims 12, 13, 15 and 16.

D4 discloses *inter alia* serine protease inhibiting compounds of formula (I) and (II), see claims 32 to 44, 48, 52 and 54 which are comprised by present claims 4, 6, 9 to 12, 15 and 16.

2.2. D5 discloses Zn-mediated serine protease inhibitors which are 2-heteroaryl-benzimidazole derivatives, see compounds APD-4, -6 and -8 which are not covered by present claims 4 and higher.

3. INVENTIVE STEP

The Applicant appears to have set himself the task of making available further protease inhibitors of the formula (I) which are (hetero)aryl-bicyclic heteroaryl derivatives.

From the prior art available so far the subject-matter comprised by D1 to D4 appears to constitute the most pertinent prior art. In view of said prior art the solution proposed in the claims of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), since D1 to D4 do not only disclose all structural features of the present subject-matter, i.e. a substituted benzimidazole or indole moiety attached at 2-position to a substituted phenyl group, but also describe the protease inhibiting properties.

In the absence of any convincing arguments and/or experimental data which would demonstrate an unexpected effect for the present compounds the subject-matter claimed appears to be an arbitrarily chosen specimen from said prior art, i.e. it is merely one way of carrying out the prior teaching and provides no new invention.

4. INDUSTRIAL APPLICABILITY

Claims 11 and 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

ad section VI

WO 99 26933 A (AXYS PHARMACEUTICALS, INC.) with priority dates

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/30302

26.11.1997 and 17.11.1998, filing date 25.11.1998 and published on 3.06.1999

WO 99 26941 A (AXYS PHARMACEUTICALS, INC.) with priority dates
26.11.1997 and 17.11.1998, filing date 25.11.1998 and published on 3.06.1999

The priority documents pertaining to the present application were not available at the time of establishing this first written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-document(s) cited in the international search report could become relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.

ad section VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents of the international search report is not mentioned in the description, nor are these documents identified therein.
2. The compound of example 200, see formula given on page 50, obviously does not correspond to the ex.no. 200 mentioned in the table on page 56.
Additionally ex. no. 119 given in the table on page 52 does not correspond to the compound name for said example on page 620
3. On page 68 there appears a reference to a table 2a which is non-existent, see lines 32/33.
Additionally pages 70 to 73, 75 contain further ambiguous references to table 2a which, however, starts only with ex. no. 301.
4. The units "psi" employed on page 72 are not additionally expressed in terms of the units stipulated by Rule 10.1/(a)/and/(b) PCT.
5. The prolific use of "and the like" throughout the specification is considered

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/30302

irrelevant and thus superfluous, cf. Rule 9.1(iv) PCT.

6. The term "celite" used on pages 32 (twice), 46, 69, 134 and 146 appears to be a registered trade mark.

ad section VIII

1. In claim 8 the expression "compound with methane" appears to be ambiguous.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 31 August 2000 (31.08.00)	
International application No. PCT/US99/30302	Applicant's or agent's file reference 217PCT
International filing date (day/month/year) 17 December 1999 (17.12.99)	Priority date (day/month/year) 18 December 1998 (18.12.98)
Applicant ALLEN, Darin, Arthur et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 14 July 2000 (14.07.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Authorized officer

Jean-Marie McAdams

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

KATHARDEKAR, Vinit, G.
Axys Pharmaceuticals, Inc.
180 Kimball Way
South San Francisco, CA 94080
ETATS-UNIS D'AMERIQUEDate of mailing (day/month/year)
24 October 2000 (24.10.00)Applicant's or agent's file reference
217PCTInternational application No.
PCT/US99/30302

IMPORTANT NOTIFICATION

International filing date (day/month/year)
17 December 1999 (17.12.99)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

MACKMAN, Richard, Laurence
2240 Bay Street, Apt. 302
San Francisco, CA 94403
United States of America

State of Nationality

GB

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

MACKMAN, Richard, Laurence
2240 Bay Street, Apt. 302
San Francisco, CA 94123
United States of America

State of Nationality

GB

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Genève 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

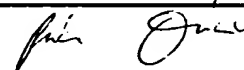
Ellen Moyse

Telephone No.: (41-22) 338.83.38



A bejelentés ügyszáma: P0104987

Kat.	P C T	A releváns iratok azonosító adatai	A vonatkozó igénypontok száma	A bejelentés osztályjelzete NSZO6
X	*	Lásd a mellékelt PCT/US9930302(WO0035886) számú nemzetközi újdonságkutatási jelentés másolatát! HU 192152 B (dr. Karl Thomae GmbH. DE), 1984.04.30., kivonat, igénypontok, ábrák 1-6	C07D23518 C07D40110 C07D40310 C07D47104 C07D41710 C07D40312 C07D40112 C07D20912 C07D20918 C07D20920 A61K 314184 A61K 31404 A61P 702 C07D40510 C07D40512 C07D40910 <div>A vizsgált szakterület NSZO</div> C07D A61K

Dátum: 2002.07.16	Ügyintéző: 	
<p>* PCT-újdonságkutatási jelentésből</p> <p>A releváns iratok kategóriái:</p> <p>X: olyan irat, amely a vizsgált megoldás valamennyi lényeges jellemzőjét tartalmazza</p> <p>Y: olyan irat, amely egy vagy két irattal kombinálva magában foglalja a vizsgált megoldás valamennyi lényeges jellemzőjét</p> <p>A: a technika állását meghatározó irat</p>	<p>O: olyan irat, amely nyilvános gyakorlatbavételre, használatra, szóbeli közlésre, kiállításra vagy más módon történő ismertetésre utal</p> <p>P: olyan irat, amely a magyar bejelentés napja előtt, de az igényelt elsőbbség napján vagy azt követően került nyilvánosságra</p> <p>E: olyan korábbi elsőbbségű magyar szabadalmi vagy használati mintaoltalmi leírás, amely a</p>	<p>vizsgált bejelentés elsőbbségi napját követően került nyilvánosságra</p> <p>D: olyan irat, amelyet a vizsgált megoldás leírásában a technika állásának ismertetésénél a bejelentő idéz</p> <p>&: azonos szabadalmi családba tartozó irat /analóg/</p>